REMARKS

Applicant wishes to thank Examiners Lucas and Housel for the courtesy extended to the inventor, Dr. Benoit Gamain, and the delegates, Joseph Conrad and Peter Soukas, of National Institutes of Health, which has been duly delegated responsibility under the authority of The Government of the United States of America, as represented by the Secretary, Department of Health and Human Services, as Assignee, and the representative, Nancy Vensko, attorney of record, on October 17, 2003. The Interview Summary Form PTOL-413 summarizes the discussions held at the personal interview. The present response to the outstanding Office Action includes the substance of the Examiner Interview.

A. Disposition of Application

By this amendment, Applicant has canceled Claims 1-11, 22, 23, 25-31 and 34-55, as being withdrawn from consideration, and 13-20, 24, 32, and 33, all without prejudice, amended Claims 12 and 21, and added Claims 56-61. Thus, Claims 12, 21, and 56-61 are pending. Applicant seeks rejoinder of Claims 59-61 under In re Ochiai and In re Brouwer.[1] This amendment is presented to make explicit that which was implicit in Claims 12 and 21. Support for the amendment is found throughout the Specification as discussed below. Additionally, per MPEP 608.01, the Specification has been amended to delete the embedded hyperlink. Turning to the figures, Fig. 1C has been conformed to the informal drawings as originally filed in PCT/US00/24195 on September 1, 2000, to which the instant application relates back. No new matter has been added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

B. Support for the Amendment

Malaria during the first pregnancy causes a high rate of fetal death. As disclosed in the Specification and the post-filing date art of Buffet et al., PNAS 96: 12743 (Oct 1999), of record and re-attached,[2] a domain within a *Plasmodium falciparum* erythrocyte membrane protein 1 (Pfemp1)

---

[1] "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)" March 26, 1996 Official Gazette.

[2] According to Buffet et al., the sequence reported in the paper was deposited in the GenBank database as accession no. AJ133811, which is made of record in the attached IDS. The direct submission is indicated to be 23 Apr 1999. The effective filing date of the instant application is 1

mediates binding to chondroitin sulfate A (CSA), a receptor for parasites in the placenta. The investigators cloned a *var* gene, FCR3-CSA, assigning it SEQ ID NO:1 (gene) and SEQ ID NO:2 (protein), which was present in CSA-binding parasitized red blood cells (PRBCs). The gene had eight receptor-like domains (Spec. at Fig. 1), each of which was expressed on the surface of Chinese hamster ovary cells and was tested for CSA binding. The results focused on a Duffy-binding-like (DBL) domain, DBL3, having the amino acid sequence of residues 1279-1554 of SEQ ID NO:2 (Spec. at Fig. 1B). CSA linked to biotin used as a probe demonstrated that the DBL3 domain bound CSA, but not chondroitin sulfate C (CSC) linked to biotin, a negatively charge sugar that does not support PRBC adhesion (Spec. at Fig. 2A). Furthermore, CSA, but not CSC, blocked the interaction with DBL3 (Spec. at Fig. 2B). Thus, the DBL3 domain displays the same binding specificity as PRBCs. Immunization with the DBL3 domain induced pan-reactive and adhesion-blocking antibodies against PRBCs, as disclosed in the post-filing date art of Costa et al., JID 188: 153 (2003), made of record in the attached IDS. Additionally, structure-function analysis of the DBL3 domain localized the minimal CSA binding region to a 67-residue fragment, as disclosed in Gamain et al., in press, made of record in the attached IDS. These findings have application for a vaccine against malaria.

This amendment is presented to make explicit that which was implicit in Claims 12 and 21. Support for the amendment is found throughout the Specification, for example, as follows.

Sept 1999. The direct submission is not, however, prior art under 102(a) because of the following. Under MPEP 715.01(c), unless it is a statutory bar (which it is not), a rejection based on a publication may be overcome by a showing that it is a publication of applicant's own work. Here is the showing. The direct submission indicates it was made by Dr. Scherf. This is the same Dr. Scherf who is a co-inventor of the instant application. Consequently, there is no need to make a showing that any co-authors who were not additionally named as co-inventors were merely working under the direction of the co-inventors to remove the publication as a reference under 35 USC 102(a) in the form of an In Re Katz Declaration. Rather, any co-author of the direct submission is a co-inventor of the instant application, thus the direct submission is a publication of applicant's own work. In conclusion, a rejection under 35 USC 102(a) as being anticipated by the direct submission cannot stand.

Spec. at 4:17-21:

Another aspect of the invention includes the use of therapeutic or prophylactic agents (e.g., FCR3.varCSA or fragments of FCR3.varCSA, A4 tres DBL3-γ (SEQ. ID. No.: 9) and ItG2-CS2 DBL2-γ (SEQ. ID. No.: 11) or nucleic acids encoding these compositions) to modulate adhesion to CSA and/or to generate an immune response in a patient.

Spec. at 5:21-26:

Further, methods of treatment and prevention of malaria, specifically maternal malaria, are provided. Some methods of treatment and prevention of maternal malaria, involve identifying a subject in need of an agent that inhibits the association of a varCSA molecule (e.g., FCR3.varCSA) with CSA and administering to said subject a therapeutically effective dose of an agent that either inhibits adhesion of the varCSA molecule to CSA and/or promotes an immune response in a patient.

Spec. at 10:12-15:

Further, in some embodiments, nucleic acids encoding wild-type or mutant FCR3.varCSA or fragments of FCR3.varCSA or complements thereof are transfected and expressed in cells so as to modulate FCR3.varCSA-mediated adhesion or to induce an immune response or both.

Spec. at 10:16-23:

According to other aspects, the modulation of FCR3.varCSA-mediated adhesion is achieved by using a modulator that is a protein-based embodiment. For example, FCR3.varCSA is delivered to cells by liposome-mediated transfer so as to raise the intracellular concentration of FCR3.varCSA and thereby promote FCR3.varCSA-mediated adhesion to CSA or, alternatively, wild-type or mutant FCR3.varCSA or fragments of FCR3.varCSA (e.g., DBL3 and/or CIDR1) are delivered to cells by

liposome-mediated transfer so as to inhibit FCR3.varCSA-mediated adhesion to CSA or to induce an immune response or both.

Spec. at 10:29-31:

Approaches in rational drug design can be employed, for example, to identify novel agents that interact with FCR3.varCSA so as to modulate FCR3.varCSA-mediated adhesion or that can be used to induce an immune response in a patient.

Spec. at 31:24-30:

The FCR3.varCSA fragments can be less than or equal to 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2,500, 3000, 3,500, or 3,542 amino acids in length.

Spec. at 32:17-19:

Because the region of FCR3.varCSA (e.g., a region within a DBL3 domain) that mediates CSA adhesion can be quite small (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 18, 20, 22, 25, 30 amino acids in length) ...

Spec. at 37:8-11:

Further, peptidomimetics that structurally and/or functionally resemble a peptide embodiment (e.g., FCR3.varCSA or fragments of FCR3.varCSA) can be made and evaluated for their ability to interact with CSA in a characterization assay or to induce an immune response in a subject.

Spec. at 38:4-12:

Peptides used to induce specific antibodies can have an amino acid sequence consisting of at least three amino acids, preferably at least 10 or 15 amino acids. Desirably, short stretches of amino acids encoding fragments of a varCSA molecule (e.g., FCR3.varCSA, A4 tres DBL3-γ, or ItG2-CS2 DBL2-γ) are fused with those of another protein such as keyhole limpet hemocyanin and antibody is produced against the chimeric molecule. While antibodies capable of specifically recognizing a varCSA molecule, for example, can be generated by injecting into mice synthetic 3-mer, 10-mer, and 15-mer peptides that correspond to the particular protein sequence, a more diverse set of antibodies can be generated by using a recombinant or purified protein embodiment.

Spec. at 40:22 - 41:6:

Additionally, FCR3.varCSA, fragments of FCR3.varCSA, A4 tres DBL3-γ, or ItG2-CS2 DBL2-γ can be used to induce antibody production in humans. That is, these peptides whether made chemically or as detailed above, can be used as an antigen or vaccine so as to elicit an immune response in a patient. Accordingly, FCR3.varCSA, fragments of FCR3.varCSA, A4 tres DBL3-γ, or ItG2-CS2 DBL2-γ can be joined to or administered with another protein, carrier, support, or adjuvant so as to generate a pharmaceutical or vaccine that will induce potent immune response. Additionally, nucleic acids encoding FCR3.varCSA, fragments of FCR3.varCSA, A4 tres DBL3-γ, or ItG2-CS2 DBL2-γ can be administered by themselves or with FCR3.varCSA, fragments of FCR3.varCSA, A4 tres DBL3-γ, or ItG2-CS2 DBL2-γ and, as above, can be joined to or administered with a protein, carrier, support, or adjuvant. These nucleic acids can be administered "naked" or can be incorporated into vectors. Vaccination protocols can include, for example, identifying a subject in need of a vaccine (e.g., pregnant women in regions populated with *P. falciparum*) and administering to said subject a therapeutically effective amount of either a protein or a nucleic acid-based vaccines or combinations of protein and nucleic acid vaccines.

Spec. at 57:18-24:

Biotechnological tools and components to prophylactic and therapeutic agents desirably provide FCR3.varCSA, fragments of FCR3.varCSA, A4 tres DBL3-γ, or ItG2-CS2 DBL2-γ antibodies or antibody fragments that recognize epitopes on these molecules, fusion proteins containing these molecules, nucleic acids encoding these molecules (and complementary nucleic acids thereof) in such a form or in such a way that a sufficient affinity, modulation of a varCSA-CSA complex formation or induction of an immune response is achieved.

Spec. at 58:3-10:

A multimeric agent (synthetic or natural) that modulates the formation of a varCSA-CSA complex or induces an immune response is obtained by joining FCR3.varCSA, fragments of FCR3.varCSA, A4 tres DBL3-γ, or ItG2-CS2 DBL2-γ antibodies or antibody fragments that recognize epitopes on these molecules, fusion proteins containing these molecules, nucleic acids encoding these molecules (and complementary nucleic acids thereof), collectively referred to as "FCR3.varCSA modulating agents", "varCSA modulating agents" or "modulators", to a macromolecular support.

Spec. at 72:5-10:

The varCSA modulating agents described herein are suitable for treatment of subjects either as a preventive measure to avoid maternal malaria, or as a therapeutic to treat subjects already afflicted with the disease. Although anyone could be treated with the agents of the invention as a prophylactic, the most suitable subjects are people at risk for maternal malaria. Such subjects include, but are not limited to, pregnant women living in regions of the world populated with *P. falciparum.*

Spec. at 75:6-19:

Several methods of treatment and prevention of maternal malaria, which involve administration of the pharmaceutical embodiments of the invention are provided. In

these aspects of the invention, FCR3.varCSA, fragments of FCR3.varCSA, A4 tres DBL3-γ, or ItG2-CS2 DBL2-γ, nucleic acids encoding these molecules, and agents that interact with a varCSA-CSA complex are incorporated into pharmaceuticals and are administered to patients in need. Because aspects of the invention that incorporate a varCSA molecule or fragments thereof can both interrupt varCSA mediated adhesion and stimulate an immune response to these polypeptides, significant therapeutic and prophylactic benefit can be achieved by administration of these agents to patients in need. Thus, in some contexts, a therapeutic protocol can also be termed a method of vaccination. By one approach, a subject at risk for contracting maternal malaria or a subject infected with *P. falciparum* is identified by conventional techniques or the diagnostic assays described above and then a therapeutically or prophylactically beneficial amount of a varCSA molecule or fragment thereof is administered.

Support for the amendment having been pointed out in the Specification as discussed above, Applicant reiterates that no new matter has been added.

C. **Compliance with Formalities**

The Patent Office objected to Claims 12, 16, 18-21, and 24 because of certain informalities. The claims must be in compliance with the formalities. This amendment is presented to make explicit that which was implicit in Claims 12 and 21, thus (except for Claims 12 and 21) the claims have been canceled. As for Claims 12 and 21, the claims were objected to because reference to a disclosed sequence should use the introductory term "SEQ ID NO:" followed by the number of the referenced sequence as provided in the sequence listing. Appropriate correction was required. "SEQ ID NO.:" has been corrected to omit the extra period. By virtue of correction of Claims 12 and 21, and cancellation of the remaining claims, all pending claims are in compliance with the formalities.

D. Compliance with 35 USC 101, Utility

The Patent Office rejected Claims 20 and 24 under 35 USC 101 as failing to meet the utility requirement. The claims must meet the utility requirement. This amendment is presented to make explicit that which was implicit in Claims 12 and 21, thus (except for Claims 12 and 21) the claims have been canceled. By virtue of pendency of Claims 12 and 21, and cancellation of the remaining claims, all pending claims are in compliance with 35 USC 101 as meeting the utility requirement.

E. Compliance with 35 USC 112/2, Definiteness

The Patent Office rejected Claims 13-17, 19, 20, 21, and 24 under 35 USC 112/2 as being indefinite. The claims must meet be definite. This amendment is presented to make explicit that which was implicit in Claims 12 and 21, thus (except for Claims 12 and 21) the claims have been canceled. As for Claim 21, the claim was rejected because the claim recited a domain of an unknown SEQ ID NO. Appropriate correction was required. "SEQ ID NO:2" has been identified. By virtue of correction of Claim 21, pendency of Claim 12, and cancellation of the remaining claims, all pending claims are in compliance with 35 USC 112/2 as meeting the definiteness requirement.

F. Compliance with 35 USC 112/1, Written Description

The Patent Office rejected Claims 18, 19, 24, 32, and 33 under 35 USC 112/1 as failing to meet the written description requirement. The claims must meet the written description requirement. This amendment is presented to make explicit that which was implicit in Claims 12 and 21, thus (except for Claims 12 and 21) the claims have been canceled. By virtue of pendency of Claims 12 and 21, and cancellation of the remaining claims, all pending claims are in compliance with 35 USC 112/1 as meeting the written description requirement.

G. Compliance with 35 USC 112/1, Enablement

The Patent Office rejected Claims 13-17, 18, 19, 20, and 24 under 35 USC 112/1 as failing to meet the enablement requirement. The claims must meet the enablement requirement. This amendment is presented to make explicit that which was implicit in Claims 12 and 21, thus (except for Claims 12 and 21) the claims have been canceled. By virtue of pendency of Claims 12 and 21,

and cancellation of the remaining claims, all pending claims are in compliance with 35 USC 112/1 as meeting the enablement requirement.

H. Compliance with 35 USC 102, Novelty

The Patent Office rejected Claims 13-17 under 35 USC 102(b) as being anticipated by Sim et al., WO 96/40766, published 19 Dec 1996. The Patent Office rejected Claims 18 and 24 under 35 USC 102(a) as being anticipated by Reeder et al., PNAS 96: 5198 (Apr 1999). The Patent Office rejected Claims 18, 19, 20, and 24 under 35 USC 102(a) as being anticipated by Scherf et al., EMBO Journal, 17: 5418 (15 Sept 1998). The claims must be free of the prior art. This amendment is presented to make explicit that which was implicit in Claims 12 and 21, thus (except for Claims 12 and 21) the claims have been canceled. By virtue of pendency of Claims 12 and 21, and cancellation of the remaining claims, all pending claims are in compliance with 35 USC 102 (and 103) as meeting the requirement to be free of the prior art.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 11/3/03

By: _____

Nancy W. Vensko
Registration No. 36,298
Attorney of Record
Customer No. 20,995
(805) 547-5585

AMEND
O:\DOCS\NWV\NWV-9168.DOC
110303